P H Y S I O L O G Y

Enhanced responsiveness of GhsrQ343X rats to ghrelin results in enhanced adiposity without increased appetite

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Abstract

The ability of the gut hormone ghrelin to promote positive energy balance ismediated by the growth hormone secretagogue receptor (GHSR). GHSR is a G protein–coupled receptor (GPCR) that is found centrally and peripherally and that can signal in a ligand-independent manner basally or when heterodimerized with other GPCRs. However, current Ghsr knockout models cannot dissect ghrelin-dependent and ghrelin-independent signaling, precluding assessment of the physiological importance of these signaling pathways. An animal model carrying a Ghsr mutation that preserves GHSR cell surface abundance, but selectively alters GHSR signaling, would be a useful tool to decipher GHSR signaling in vivo. We used rats with the GhsrQ343X mutation (GhsrM/M), which is predicted to delete the distal part of the GHSR carboxyl-terminal tail, a domain critical for the signal termination processes of receptor internalization and b-arrestin recruitment. In cells, the GHSR-Q343X mutant showed enhanced ligand-induced G protein–dependent signaling and blunted activity of processes involved in GPCR signal termination. GhsrM/M rats displayed enhanced responses to submaximal doses of ghrelin or GHSR agonist. Moreover, GhsrM/M rats had a more stable body weight under caloric restriction, a condition that increases endogenous ghrelin tone, whereas under standard housing conditions, GhsrM/M rats showed increased body weight and adiposity and reduced glucose tolerance. Overall, our data stress the physiological role of the distal domain of GHSR carboxyl terminus as a suppressor of ghrelin sensitivity, and we propose using the GhsrM/M rat as a physiologicalmodel of gain of function in Ghsr to identify treatments for obesity-related conditions.

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